An incredible paper was just published (thank you David Wiseman for the heads up)

It's incredible in terrifying ways.

Jessica Rose
Jun 18

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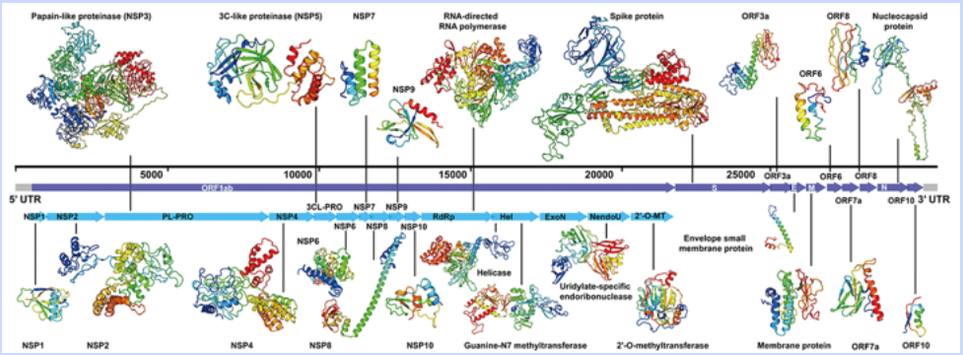
Please read this paper entitled: "Neurotoxic amyloidogenic peptides in the proteome of SARS-COV2: potential implications for neurological symptoms in COVID-19". It was published in Nature Communications on June 13, 2022.[1]

The bottom line of this incredible work is that there are two amyloidogenic proteins in the Open Reading Frames (ORF) 6 and 10 from SARS-nCoV-2 (the ORF-10 one does not have a homologue in SARS-nCoV - that means it's unique to SARS-nCoV-2), that form crystalline amyloid structures independently, and together, at room temperature!, very quickly, and that these structures induce programmed cell death in neural cells.

Before I unpack this article, I want to say something. I think this was able to be published in this prestigious journal for 2 reasons: 1. this is about COVID-19 (SARS-nCoV-2) and 2. this is about the ORFs and NOT the spike protein amyloidogenic peptides.

Before I start, here's the genome of SARS-nCoV-2 and some information on the ORF-6 [2] [3] [4] which is a highly pathogenic protein in and of itself.[5]



Modeling of the SARS-COV-2 Genome using I-TASSER.
zhanglab.dcmb.med.umich.edu

Let's start. These amazing people did the same kind of thing as described in this paper that I described here. To briefly summarize, they used amyloid prediction algorithms (TANGO) and other bioinformatics tools (ZIPPER) to provide choices of residue windows of specific lengths. They found 2 contender amyloidogenic peptides that reside in the SARS-nCoV-2 ORFs 6 and 10: ILLIIM and RNYIAQVD, respectively. These were the two that they decided to synthesize and study because of their predicted amyloidogeneticity potential.

> Amyloid aggregation prediction algorithms identified two short peptides from ORF6 and ORF10 that are likely to form amyloids.

My readers know all too well by now (because you're amazing), that amyloid proteins are really beta-sheet rich. Below is Figure 1 from the paper which shows where the peptides reside in the respective ORFs (ORF-6 and ORF-10) and their beta sheet propensities.

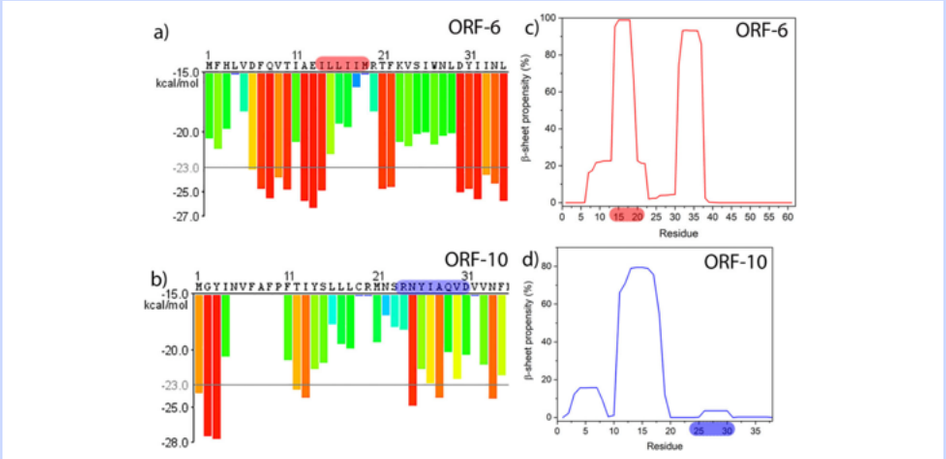


Fig. 1 Output from amyloid assembly prediction software for SARS-CoV-2 ORF6 and ORF10 sequences. a, **b** Outputs from amyloid predicting algorithm ZIPPER identifying hexapeptide fragments predicted to form steric zippers nucleating the assembly of amyloid fibrils. Hexapeptides with Rosetta energies below −23 kcal mol^{-1} are predicted to be highly amyloidogenic and are shown with red bars. **c**, **d** Outputs from amyloid predicting algorithm TANGO indicating sequence regions of high propensity to form β-sheets.

> Nanoscale imaging reveals both peptide sequences self assemble into polymorphic amyloid assemblies.

Two things struck me about the conditions under which the structures assembled: assembly happened at room temperature and it happened immediately.

> Atomic force microscopy (AFM) imaging of the two peptide assemblies revealed that both peptides assembled at 37 °C almost immediately at 1 mg mL−1 (Supplementary Figs. 1 and 2) into a highly polymorphic mixture of nanofibrous and crystalline structures.

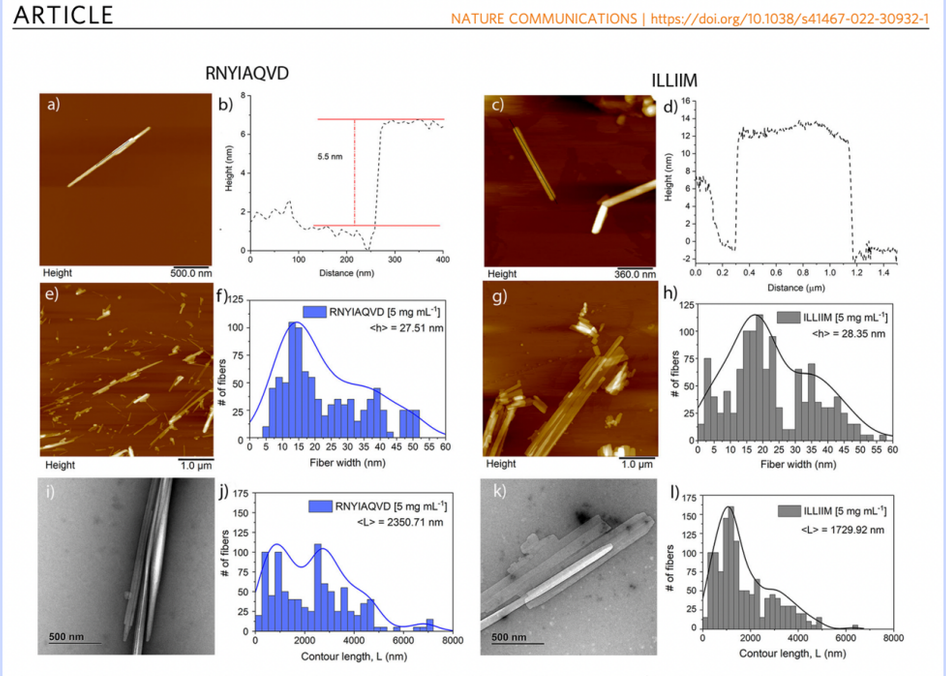


Fig. 2 Atomic force and transmission electron microscopy images of peptide assemblies at 5 mg mL^{-1} incubated for 24 h. a–d AFM images and linescans showing variation in assembly width and assembly stacking for both peptides, all AFM images are taken at 512 × 512 scan lines × pixels, at a scanning speed of 0.5 Hz displayed at a *z*-height of 40 nm using a black-golden-white colour gradient. **e–h** additional lower magnification AFM images of both assemblies and corresponding fibre width quantitative analysis. **i–l** TEM images of the two peptide assemblies, and contour length analysis of the two assemblies (from AFM data). All statistical analysis was performed on datasets including at least 900 assemblies, all histogram fitting was performed in Origin Pro using the Kernel Smooth fitting parameters with Scott Bandwith, scaled to 100% of the maximum intensity of the histogram. All images are representative images taken from three independent experiments. Additional examples of TEM and AFM images from other independent experiments can be found in the Supplementary information (Supplementary Figs. 3–6).

Aren't those images incredible! The needle-like structures that each peptide formed independently were slightly different whereby:

> ILLIIM tends to form very large (2–3 μm in width) multi-laminar crystalline assemblies (Fig. 2g), whereas RNYIAQVD predominantly forms long linear needle-like structures.

Another thing that struck me about what they found was these peptides that assemble into these structures 'tend[ed] to stack on top of each other forming multi-laminar structures'.

The authors used all sorts of techniques such as "X-ray scattering, spectroscopic characterization, fluorescent microscopy and molecular modeling confirm the amyloid nature of the assemblies".

In light of these incredible findings, there still may not be an effect *in vivo* or in the living organisms like humans. They hypothesized toxicity to human neurons and investigated this hypothesis using a human cell line called SH-SY5Y exposed to both ILLIIM and RNYIAQVD. They found that ILLIIM and RNYIAQVD triggered late-stage apoptosis in the cells (programmed cell death) where ILLIIM did so prominently as very low concentrations (0.04 mg mL−1 vs 0.15 mg mL−1 for ILLIIM and RNYIAQVD, respectively.

Summary: Two peptides from ORF-6 and ORF-10 of SARS-nCoV-2 induce apoptosis in human neural cells.

They subsequently conclude that this be what's causing all the neurological problems associated with COVID-19.

> The cytotoxicity and protease-resistant structure of these assemblies may result in their persistent presence in the CNS of patients post-infection that could partially explain the lasting neurological symptoms of COVID-19.

I know what you're thinking.

Let's ask the three questions of our lifetimes, shall we?

Question 1: Are amyloidogenic peptides residing in the SARS-nCoV-2 spike protein and are they capable of inducing apoptosis in neural cells and/or other cells types?

Question 2: Since the modified spike proteins, used to construct the LNP-encased payload in the Moderna and Pfizer injectable biological products, are derived from the SARS-nCoV-2 spike, do these proposed amyloidogenic properties carry over?

Question 3: If the modified spike protein in the COVID-19 injectable products contain amyloidogenic peptides capable of assembling into amyloid structures, is this why we are seeing such systemic neurological, hepatological, cardiovascular and reproductive damages with regard to adverse event reports in databases such as VAERS, Eudra and Yellowcard?

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1 Charnley, M., Islam, S., Bindra, G.K. *et al.* Neurotoxic amyloidogenic peptides in the proteome of SARS-COV2: potential implications for neurological symptoms in COVID-19. *Nat Commun* **13**, 3387 (2022). https://doi.org/10.1038/s41467-022-30932-1.

2 Baric Ralph A. et al., Severe Acute Respiratory Syndrome Coronavirus Open Reading Frame (ORF) 3b, ORF 6, and Nucleocapsid Proteins Function as Interferon Antagonists. Journal of Virology. 2007. Vol. 81, No.2 https://journals.asm.org/doi/10.1128/jvi.01782-06?permanently=true.

3 Lei, X., Dong, X., Ma, R. *et al.* Activation and evasion of type I interferon responses by SARS-CoV-2. *Nat Commun* **11**, 3810 (2020). https://doi.org/10.1038/s41467-020-17665-9.

4 Lee, JG., Huang, W., Lee, H. *et al.* Characterization of SARS-CoV-2 proteins reveals Orf6 pathogenicity, subcellular localization, host interactions and attenuation by Selinexor. *Cell Biosci* **11**, 58 (2021). https://doi.org/10.1186/s13578-021-00568-7.

5 Nasim Kheshtchin, Parisa Bakhshi, Samaneh Arab, Maryam Nourizadeh, Immunoediting in SARS-CoV-2: Mutual relationship between the virus and the host, International Immunopharmacology, 105, (108531), (2022).

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Martin I Jun 18 Liked by Jessica Rose

Yikes, spikes! Or rather polymorphic amyloid assemblies!

I got over covid a week or two ago, and don't feel particularly stupider now than usual, but that isn't saying much.

I may have indeed been struck in the head with those striking polymorphic amyloid assemblies.

This nightmare just keeps getting worse and worse.

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Holy poo Batgirl. Thanks. Will get this out. Rollin' rollin' rollin'

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